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THE ETIOLOGY OF SPRUE.

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TROPICAL DISEASES AS THEY EXIST IN PORTO RICO.

(From the Institute of Tropical Medicine and Hygiene of Porto Rico.)

THE object of this paper is to demonstrate that the species of *Monilia* first described by me in March, 1915¹ is the determining etiological factor in sprue, and to suggest that this species be recognized as *Monilia psilosis*, Ashford, 1914.

It was stated in a paper presented by the writer May 13, 1915, before the annual meeting of the Association of American Physicians,² that Dr. Isaac Gonzalez, member of the Institute of Tropical Medicine and Hygiene of Porto Rico, working with an antigen prepared from three strains of this species furnished him by me, had demonstrated in 4 cases of sprue a deviation of the complement, and that in 12 cases not sprue no such deviation could be obtained. The consensus of opinion expressed individually after that meeting was that until the demonstration of a reaction specific to this particular organism should be forthcoming the results should be considered to be due to a group reaction, thus withholding the decision as to the relation of my organism to sprue, although all other evidence, clinical, epidemiological, and mycological, as well as animal experimentation, spoke strongly for its specificity.

¹ A *Monilia* Found in Certain Cases of Sprue, Preliminary Note, Jour. Am. Med. Assoc., March 6, 1915, lxiv, 810-811.

² Studies in Moniliasis of the Digestive Tract in Porto Rico, AM. JOUR. MED. SC., 1915, No. 5, cl, 680.

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For the solution of this problem, after six months' more preliminary work, I determined to make a study of a series of 100 persons, some of whom were clinically free from sprue, some typical cases of the disease, and some whose clinical picture did not permit of a positive diagnosis, considering, however, as sprue only such cases as should prove themselves positive, clinically, mycologically, and serologically. Only very slight and justifiable departures have been made from this plan, as will be seen later.

The interpretation of the deviation of the complement, as is well known, is not only a matter into which the personal equation enters, but such highly specialized laboratory work requires long



FIG. 1.—Non-specific commensal from a case of pellagra. Case CCXXIa. Note short articles, heavily nucleated and granular yeasts and large size of the elements. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

experience, careful technic, and, in short, genuine ability. It was evident that such reactions should be made by some such person who should have no knowledge whatever of the clinical and mycological history of the case, and who would simply receive the blood of the patient without any inkling of such history, without even seeing the patient. Dr. Gonzalez Martinez, whose previous work has been mentioned above, was on a visit to the North, and the uncertainty of my being able to continue this research without interruption was very great. I was fortunate enough to associate myself in the study of this series with Dr. Carl Michel, of the U. S. Public Health Service, recently assigned to duty for his service in San Juan, and now a collaborator in this institute. This serologist

had spent a long time, previous to his arrival here, in doing this very kind of blood work in syphilis and experimentally in other diseases, and was peculiarly prepared by his experience to fill all of the requisites desired. The results, of course, have been recorded as received from him and incorporated with the clinical and mycological history of each case. His own report appears elsewhere in this JOURNAL, and his technic and conclusions are expressed individually.

So while there has been a great effort made to elucidate the facts in this series, there has been no straining after-effect nor any divergence from the avowed intention to let these facts speak for themselves.



FIG. 2.—Wild yeast found in feces. Case CLXXVIB. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

The work has been, as can be imagined, a very arduous one. Not only was it necessary to obtain a clear history in which neither patient nor physician would unconsciously accentuate important symptoms, but a thorough mycological study of the tongue-scrapings and feces was exacted in each case. This latter work was most time-consuming, as plate cultures had to be made of all *Monilia*-like colonies, and as frequently more than one species was found, and each had to be plated out and run through the proof media, several hundred such cultures were necessary.

With two or three exceptions all of the series were personal cases of the writer, and were seen by him and treated day by day, week by week, thus adding the control of the clinician to the laboratory findings.

The routine observed was as follows: After the clinical history had been taken, cultures from scrapings of the tongue on glucose agar slants and streak cultures from the feces in glucose-agar plates were made. Suspicious colonies were plated out for pure culture on a 4 per cent. glucose-agar (Sabouraud), + 2 acidity. These plates were incubated for from three to five days. At about the same time a technician of this laboratory, Mr. Jose Loubriel, secured 5 c.c. of blood from a vein of the arm, the blood tube was given a key designation, and it was delivered to Dr. Michel for serological examination after previous centrifugalization and decompensation. The plate cultures were now examined with a hand



FIG. 3.—Yeasts and hyphae, *Monilia psilosis*. Case CCXXXIIIb. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

glass and all *Monilia*-suspicious colonies were fished. This process is an important one and taxes the skill of the operator, as fine differences in color, consistency, and polish of the surface make for success. The selection of the right creamy colony when small is most difficult, and often impossible. Only after repeated plating of feces in quiescent cases of sprue was it possible to demonstrate *Monilia psilosis*, and in some, as will be seen, they have not yet been isolated, due to the fact that the wrong colony has been fished or that the surface yeast production in the infected intestinal canal is insufficient to give colonies in a limited number of plates. It is well known that in the quiescent stage of sprue, where neither tongue nor intestine is acutely inflamed, only the past history and present

euchlexia remain to justify a probable diagnosis. It has been suggested by the writer that in such cases the mycelial elements lie latent in the submucosa awaiting a favorable opportunity to bud and spread yeasts over the surface. In such cases a serological examination will demonstrate a positive reaction, generally weak, and yet only persistent effort will reveal a chance colony. Of course, it is possible that the group reaction, of which I will later speak, is responsible for the serological result, but that this is unlikely is evident from all of the overwhelming evidence presented heretofore, in previous papers, and especially from the fact that time and again repeated work reveals a stray colony of *Monilia psilosis* after several



FIG. 4.—Young cultures of *Monilia psilosis* showing typical yeasts before internal structures are characteristic. Case CXXXIIIb. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

failures in a case giving from the first a positive serological result. Cases 10, 12, 62, 77, 97, 98 and 99 are included in this series in order to be perfectly consistent, but I consider them incomplete until future search fails to reveal the organism. Even then the possibility that antibodies remain in the blood after disappearance of *Monilia psilosis* is to be considered. It should be noted, however, that 4 of these patients were cured two years ago and that their serological reaction is made now for the first time; also, that all save the last 3 have only a weak positive deviation of 25 per cent. or less. When to all of this is added the fact that antigens of other species have been used side by side with an antigen prepared from *Monilia psilosis*, with generally a negative, rarely a faintly positive

reaction, the group reaction, if present, must be considered of little importance in obscuring a diagnosis when a strongly positive reaction is obtained with *Monilia psilosis*.

Four or five days should be allowed for the development of *Monilia* colonies of sufficient size to permit even a guess at the species. Thus about ten days are required to acquire a pure culture. In each case all *Monilia*-suspicious colonies were planted separately and given a designating letter under the case number, the custom



FIG. 5.—Sabouraud agar slant. Typical culture seven days *Monilia psilosis*. Case CLIX. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

of examining the cultures previously under the high-power lens being observed in order to avoid sowing bacteria. After two days more the pure culture with its number and designating letter was sown in each of the following media:

Glucose bouillon, 4 per cent., plus 2, in U-fermentation tubes
Levulose " " " " "
Maltose " " " " "
Saccharose " " " " "
Litmus milk
Plain gelatin
Sabouraud agar slants, 4 per cent. glucose, plus 2.

All save the gelatin slabs were incubated at 32 C. As soon as a U-tube showed fermentation the percentage of gas in the blind arm was read and the media was titrated against a sterile control to determine the gain or loss in acidity by the method recommended by the Bacteriological Committee of the American Public Health Association. The special value of this morphological study of cultures sown in each of four distinct sugar media was that one failed to remember, and, by the special method of recording, failed to see what the appreciation had been in the other three, which were



FIG. 6.—Sabouraud agar slant. Old culture *Monilia psilosis*. Case 11. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

generally made along with many others on different days. Hence, when the note "typical" was found under all four media in the final grouping of reactions the check had been made on the personal equation of the mycologist's appreciation of form, etc.

All cultures in U-tubes failing to ferment were allowed to run fourteen days, at which time they were microscopically examined and titrated as above. The reaction in litmus milk was appreciated after fourteen days by comparing the sown tube with a control. An assistant covered the number of the culture with his hand and the color test was made by myself without knowing which was the

control and which the culture. Gelatin stubs were also allowed to run fourteen days before recording results. The gross appearance of the growth on Sabouraud agar slants was recorded after seven days and again in two weeks or more.

Bearing this unvarying technic in mind, let us consider the characteristics of *Monilia psilosis*:

MONILIA PSILOSIS, ASHFORD, 1914. This organism has been described by me in the two articles to which I have made reference at the beginning of this paper, but although no correction need be made of this original description some amplification must be made after several thousand more examinations.



FIG. 7.—Sabouraud agar slant. Aging three weeks *Monilia psilosis*. Case CXXIXb. (Photograph made in the Instituto of Tropical Medicine and Hygiene of Porto Rico.)

Morphology. Only after long and careful experience does the full importance of the morphology of *Monilia* become impressed on the mind. For a full year the writer was confused by the variability of form and size of the elements in even a single mount from a pure culture. *Monilia psilosis* is a large, round, bright, clean-cut yeast, from 4 to 7 micra in diameter, with at most a few granules and a nucleus. There is also usually a pale vacuole in which a

violently motile bacillus-like body darts about. The contour is always extremely sharp and well-defined, and this contour becomes a shell-like envelope in older yeasts, often thick at one pole, for then the yeast is apt to become oval. This gives it a true signet-ring appearance. The common variations are those of size, multiplication of the nucleus, and increase in the number of the motile bodies, which are then found elsewhere than in the pale vacuole. But it should always be remembered that *Monilia psilosis* is not typically a granular yeast.



FIG. 8.—Gelatin stab *Monilia psilosis*. Case LXXVI. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

With this type before us we must be prepared to consider the innumerable variations always present. Reproduction by gemination throws off great numbers of smaller yeasts, as yet imperfect in development and consequently free from the above-described internal structure, at least as far as an ordinary examination will reveal. In fact, young cultures are apt to show large round yeasts heretofore of any such structure. Intermingled with these yeasts are blunt ovals which under the hanging-drop often become hyphae. It is quite noteworthy that small nuclei and infrequent nucleation are apparently signs of a degraded type, and the patient frequently shows good resistance. Large nuclei and a tendency to mycelial

formation speak for virulent cultures. The degraded and involution forms furnish the true element of doubt in diagnosis by morphology. A degraded type can be and has been reinvested by me with all of its morphological characteristics of virulence by passage through guinea-pigs hypodermically.

If these characteristics be borne in mind the diagnosis of *Monilia psilosis* will not be so frequently made and carriers of wild yeasts or harmless commensals be heralded as carriers of syphilis.



FIG. 9.—Gelatin stab harmless commensal. Case XI. Note short fringe. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

Monilia psilosis always produces mycelial elements. There are many strains in which in glucose these elements are not easily demonstrated, but the crucial test is the gelatin stab. Without the inverted pine tree in gelatin I have never permitted myself to call a *Monilia*, *Monilia psilosis*. The articles of a hypha are clear-cut, bright, and not usually very granular. They are of all sizes, 2 to 5 micra wide and of all lengths, sometimes to more than 1000 micra. They contain pale vacuoles as do the yeasts, but these are molded to the shape of the article and lie in a line of compartments, giving the appearance of a bamboo pole sawed lengthwise. In addition, large and brilliant nuclei are often seen, at times forming a regular chain of beads from end to end. Budding takes place near the

extremity of the article and offers no peculiarity except that there is never a sterigam, one of the features of *sporotrichum*. The articles are also usually straight and not knarled, although curious involution forms are at times seen. The extremities of the article are rounded and sometimes bulge slightly. Branching is not frequent. It occurs commonly, but it is not a feature as in some species. There is a decided preponderance in some strains to short single articles otherwise characteristic. Thin structureless, presumably sterile hyphae, are seen and sometimes granular articles interpolated in a hypha whose articles are for the most part characteristic as described above.



FIG. 10.—Yeast of *Monilia psilosis* showing nuclei. Case CXLIXb. (Photograph made in the Instituto of Tropical Medicine and Hygiene of Porto Rico.)

That these characteristics are of great aid to diagnosis will be seen in my detailed records, to be later published as a bulletin of the institute, in which at different dates the morphology was described for the same culture in different sugar bouillans. The clear-cut, bright, really beautiful yeast, of large size and globular form, has served to differentiate *Monilia psilosis* from many other perfectly distinct species. A small yeast $1\frac{1}{2}$ to 3 micra in diameter is not usually *Monilia psilosis*. A highly granular, highly nucleated yeast should not be ordinarily confused with it. Least of all should a persistently oval yeast. Not that all of these types cannot be found

in a culture of *Monilia psilosis*, but they cannot be the predominating, the characteristic type.

Litmus Milk. Practically all *Monilia* I have isolated strike a bluer tone to litmus milk no matter what their species. It cannot be a good proof medium, but it has been religiously employed to exclude *Monilia albicans*, *sensu stricto*, Castellani. This fungus I have never yet isolated in Porto Rico, and Bahr's statement that the probable cause of sprue is *Monilia albicans* I cannot substantiate. In fact, *Monilia albicans* seems to mean very little culturally and even less morphologically, for no author at my disposal gives a clear mycological differential diagnosis between this organism and the many other species with which it is constantly confused. The only exception is Castellani, and even he neglects its morphology, as, in fact, he does for the most if not all of the species described in his and Chalmers' *Manual of Tropical Medicine*. But Castellani distinctly states that *Monilia albicans* coagulates and renders litmus milk acid, and that it liquefies gelatin, and these things *Monilia psilosis* never does.

Gelatin. *Monilia psilosis* and perhaps other species produce a firm, long, hair-like mycelial extension into the non-liquefied medium. The appearance has been noted as that of an inverted pine tree, and this is fairly descriptive. A *Monilia* which produces a short, fringe-like, even, close, brush-like extension from the line of the stab is apparently not *Monilia psilosis*. Much less is a stab which gives off no mycelium. The gelatin stab is a valuable adjunct to a differential diagnosis. The organism of sprue never liquefies gelatin.

Sabouraud Agar, 4 Per Cent. Glucose, Plus 2. The growth on a Sabouraud slant is daily becoming to me of more importance in identifying this species. It is typically a very faint greenish creamy, soft, elevated growth, with clearly defined borders, and, generally, a mycelial extension beneath into the medium. This greenish tinge is by no means easy to define, and the true cream color of commensals must be used to bring it out by comparison. Even more than this, *Monilia psilosis* itself presents, apparently, at times a true cream color, so that the color alone is not a dependable feature, but when the faint greenish tinge is seen the organism is probably *Monilia psilosis*, in Porto Rico. The growth, moreover, is shiny, glistening, and brilliant at times. These characteristics are best observed at the end of seven days, as after this the culture changes. Many species were isolated which were waxy, dirty gray, dull, granular, powdery, etc., and none proved to be *Monilia psilosis*. Some cultures were a brilliant orange, wine-red (Santo Domingo), coral red, or yellow, but all proved to be cryptococci and no mycelium in these vividly colored organisms has been demonstrated. They are not even *Monilia*. But there are species which must be closely related to *Monilia psilosis*, and which are difficult to distinguish from it. Especially is this so of a flat, brilliant white,

or cream-colored variety and of a heaped-up creamy growth, both without mycelial extension into the medium. After a week or so the cultures of *Monilia psilosis* vary so widely that description fails. A few of the commoner types may be briefed as follows:

1. A dirty cream, with hard, parchment-like covering.
2. A soft, dirty cream.
3. A honeycombed, muddy growth.
4. A heaped-up mass of twisted, root-like convolutions.
5. A pitted, even crater-like, dirty growth.
6. A green, honeycombed growth.

Fermentation Tests. I take this opportunity of paying a tribute to Dr. Aldo Castellani in his demand that these yeasts be always submitted to tests which will reveal the sugars they are capable of fermenting, at the same time emphasizing again his observation that we do not want to know so much what *Monilia* can be taught to ferment as to record what they actually do ferment when first isolated; in other words, their usual sugar-fermenting capacity under conditions in which they are found. Everyone knows what bacteria can be made to do in a changed environment, and if this is true of bacteria it is certainly true of the protein yeast. But at the same time that I recognize the value of Professor Castellani's proof media, I wish to protest against the creation of species on these fermentation tests alone, even against giving the dominant role to such tests in deciding species. Morphology is really more important in deciding species, and serological tests even more so, as Castellani himself states, for the latter qualification.

The only sugars normally fermented by *Monilia psilosis* are glucose, levulose, and maltose (typically, always), succharose (often), and galactose (occasionally). I could never accept as *Monilia psilosis* a yeast which fails to ferment maltose, qualifying this statement, however, by adding that in case of a probably degraded yeast of this species it is permissible to try to restore its full vigor by passage through guinea-pigs. I have thus reinvested a degraded type on several occasions (case 90 only of this series), with its lost power of mycelial production, its typical morphology, and its ability to ferment maltose; but I have ten times as frequently failed to convert what I imagined must be degraded types into *Monilia psilosis*, not only by one but by several such passages in particular cultures. Is it that a degraded *Monilia* is usually unable to recover its former characteristics, having once lost them, as in the case of the duvet-forming triocphyta; or are we handling separate but nearly related species? I believe the latter to be the case as cultural departures from *Monilia psilosis* were rare; their characteristics were generally immutable.

Monilia psilosis follows the universal rule of all *Monilia* and *Cryptococci* found here; there is no clouding of the medium when liquid. A more or less abundant sediment collects, but save when very freshly inoculated, or when gas bubbles up from the bottom

and disturbs this sediment, the medium is clear. This organism rarely produces a pellicle. A collar it does often produce at the point of contact of the surface of the liquid with the glass tube. Gas usually forms in a few days and rapidly increases. The most rapid gas producer is glucose, then levulose, then maltose, except when saccharose is fermented, in which case this sugar yields gas even more quickly than glucose. If gas is produced after seven days it usually, although by no means always, means contamination. All of these sugar media mentioned become more acid after inoculation, as evidenced by titration with phenolphthalein and a $\frac{20}{N}$ sodium hydrate solution against a control. They usually gain from plus 1.5 to plus 5 acidity, but rarely go higher.

These are therefore the routine methods by which *Monilia psilosis* has been distinguished in this laboratory. Since November, 1914, to date, February 16, 1917, nearly 300 persons, most of whom were suffering from sprue, have had their tongues and feces searched for *Monilia*, and these *Monilia* have been classified by methods above described, involving about 500 pure cultures and 8000 differential cultures, of which, in the case of the sugar media, 5000 were separately examined and their morphological characteristics recorded. All of this work, save the serological tests above noted in the last 100 cases, and the final titration of the media in the same cases, has been performed by myself, and to ensure against error I have thrown every possible doubt upon my own technique, often repeating certain cultures, especially those in maltose, over and over again. As a matter of fact, in practically every culture, the differential cultures were sown twice in succession. For these reasons I feel justified in giving what would be under other circumstances judged an unseemingly decided tone to my own views on the specificity of this organism. But I am demanding mycologically only what I have required of myself before a species could be recorded in this paper as belonging to *Monilia psilosis*. I hope that after the demonstration of all of these details we may be able to show that such strictness is unnecessary.

It has been by no means easy to find *Monilia psilosis* save in cases of true sprue with active symptoms. Some of the chronic and mild cases have been and are demanding an almost impossible amount of culture work, persistence and patience. But one thing stands out clearly to all who have gone into this laboratory to study sprue. It is unusual to find *Monilia psilosis* in a healthy man giving no history of past intestinal disturbance suspicious of sprue, and it is very easy to find it in cases with a sore tongue and diarrhea, in which case a 100 per cent. positive serological reaction for the deviation of the complement will, as a rule, quickly reward the investigator.

SUMMARY OF A STUDY OF ONE HUNDRED PERSONS EXAMINED CLINICALLY, MYCOLOGICALLY AND SEROLOGICALLY FOR SPRUE. Sixty-seven were suffering from or had suffered from clinical sprue,

and one was either a carrier or had mild sprue. Thirty-two were healthy or were suffering from other diseases than sprue.

In 61 of the 68 sprue cases *Monilia psilosis* was isolated. Of the 7 in which it was not found, 4 had been cured for at least one or two years and gave only a 50 per cent. Wassermann positive for *Monilia psilosis*. The other 3 were mild chronic cases, one with a + (25 per cent.) Wassermann and the other two with a + reaction. I believe that further culture from the feces of these seven would reveal in some or all *Monilia psilosis*, but it was desirable for many reasons to publish this study without further delay.

Seventy-one persons gave a positive deviation of the complement with an antigen of *Monilia psilosis*, all but one of the cases of clinical sprue and 4 not sprue. One of the 4 included as not sprue was a case of pellagra in whom sprue may be fairly suspected as a complication from the history; this case gave a + Wassermann reaction. The others were as follows: one a case of nervous dyspepsia with a negative Wassermann using the antigen as first prepared from case 4 but with a positive, 25 per cent. using an antigen prepared from the alcoholic extract of the same strain; one a case of bacillary enterocolitis with a + Wassermann and Noguchi (2 per cent. and 10 per cent. respectively); and one of a healthy boy with an ulcer of the leg giving a Wassermann negative and a + Noguchi.

These reactions were classified both by a percentage scale and by the fa miliar plus signs, using four phases, however, to indicate a complete absence of hemolysis, each plus having a value of 25 per cent. Of the 68 cases of clinical sprue: 8 gave a \mp ; 13 a +; 15 a ++; 11 a +++; and 20 a ++++. Only one was negative, a girl treated by me for sprue two years ago, in whom *Monilia psilosis* was then easily found. At the time of the serological examination just made I failed to find *Monilia psilosis* in scrapings from the tongue and cultures from the feces, and she was fleshy, had a good color was apparently entirely cured. In this connection it is of interest to classify these cases further with regard to their condition *at the time of the serological test*. As is well recognized, sprue is a chronic disease with acute exacerbations—now of the tongue, now of the intestine, at times of both at once. While many other conditions enter into the degree of the deviation of the complement besides the clinical symptoms (and we should remember that severe, apparently essential anaemia may be the dominant clinical note in an otherwise quiescent chronic sprue with a nevertheless strong positive serologic reaction), it seems of importance to see how far the degree of the complement deviation records with the clinical manifestations.

The cases noted in the following table under the heading "Quiescent" are not to be interpreted in the sense that active symptoms had not been personally verified by me and that the word of the patient had been taken for past symptoms justifying a diagnosis. On the contrary the diagnosis has been made on the conditions at

first found and from the intimate acquaintance of the physician with his patient throughout a long period of time, although, of course, past history has been given due weight in substantiating that diagnosis. "Quiescent" means that at the time of taking the blood the active symptoms and signs, sore tongue, and intestinal disturbance were absent. "Active" means, on the contrary, that these signs and symptoms, one or both, were present. In general therefore it is fair to conclude from an inspection of this table that in proportion to the intensity of the clinical picture so will be the deviation of the complement, with the frequent exceptions inherent in so delicate an appreciation.

DEVIATION OF COMPLEMENT IN SPRUE.

Clinical degree of sprue.	Active.					Quiescent.					Cured.				
	+	++	+++	++++	-----	+	++	+++	++++	-----	+	++	+++	++++	-----
Mild	0	0	0	0	0	5	5	5	2	3	1	1	0	0	0
Moderate	0	1	0	2	3	1	0	3	2	2	0	0	2	0	0
Severe	0	4	1	4	10	0	1	2	0	0	1	1	2	1	2

Finally, in its relation to the question of group reactions it is well to note that in 40 of the 67 cases positive for *Monilia psilosis* by the Wassermann technic the serum was tested at the same time against an antigen made from other species. The antigens used were as follows:

1. Antigen, *Monilia psilosis*, Case IV. This was the case from which the organism was first isolated in 1914 and has always been the type upon which I have checked.

2. Antigen, *Monilia psilosis*, Case CXXXV, Case 89 of the series.

3. Antigen, *Monilia* species undetermined, an apparently harmless commensal found a number of times in perfectly healthy persons.

4. Antigen, *Cryptococcus* species undetermined, orange red in color on solid media and a very frequent and harmless inhabitant of the human intestine in Porto Rico.

5. Antigen, combined species of *Monilia*, in which all *Monilia* so far isolated by me in this Island were mixed.

Of 21 reactions of Wassermann type performed with antigens 3 and 4, those with the antigen of *Monilia psilosis* being positive, 21 were negative. The other three all gave a 100 per cent. positive for *Monilia psilosis* and a + only for one or the other of the antigens of 3 and 4. Of 16 Wassermann reactions performed with antigen 3 alone, 15 were negative and one with a 100 per cent. positive for *Monilia psilosis* gave a +.

The Clinical Histories. These have been briefed from a question form identical for each case.

THE AGE.

Years.	Cases.
1 to 9	1
10 to 15	1
16 to 30	20
31 to 50	33
Over 50	7

It might be deduced from this table that sprue is *par excellence* a disease of the prime of life, but in reality it is not so restricted. On

account of the difficulties attendant upon obtaining sufficient blood for the serological tests in the very young, cases under fifteen years had to be usually omitted. Specific intestinal moniliasis is fully as common among children as adults. A goodly proportion of acute and chronic enterocolitis of children in cities, in a country where practically all milk is boiled, are due to *Monilia psilosis*.

Sex. Males, 26 cases; females, 42 cases. Whether this proportion will hold good for a larger number is problematical. In Porto Rico, as in most countries, women eat more sweets than men, and their tendency to live their lives within four walls undoubtedly lessens their resistance to the effects of a chronic infectious disease like sprue.

Color. Whites, 55; mulattos, 13. Sprue seems to be a rare disease among negroes.

COUNTRY.

Porto Rico	48 cases
United States	10 "
Spain	4 "
Syria	3 "
English Antilles	1 case
Santo Domingo	1 "
Venezuela	1 "

All foreigners give a clear history of having been infected a short while after reaching Porto Rico, with the exception of Dominicans. In Santo Domingo the disease is believed to be prevalent in towns, as seen from many cases outside of this series. That sprue is more prevalent among foreigners is clear, as the proportion to Porto Rican residents is not above 1 to 50 of the population in San Juan, and the type of the disease in the former is apt to be more severe.

ECONOMIC POSITION.

Poor	8 cases
In modest circumstances but able to secure an ample food supply	27 "
Well-to-do	28 "
Wealthy	5 "

Sprue is an urban disease and is much more prevalent among those who are able to live well. Therein it differs from pellagra. Its comparative rarity in the country districts among the poor laborers is seen in the result of a careful survey of 10,140 country people in Utuado in 1914, among whom only 11 cases of complete sprue and 19 doubtful cases were seen. The majority of these 30 cases lived in the town of Utuado and not in the country.

OCCUPATION.

Motorist	1	Mayor Domo Sugar Central . . .	1
Housewife	31	Petty Officer, Federal Service . .	1
Fruit grower	1	Laborer	2
Sugar planter	2	School girl	2
Merchant	2	Society girl	1
Pedlar	1	Chief Engineer, Sugar Central . .	1
Servant	2	Policeman	1
School teacher	5	Statenman	1
Convict	1	Supervisor schools	1
Navy Officer	1	Collector rents	1
Sister of Charity	2	Artisan	1
Sergeant, U. S. Army	1	Justice of Court	1
Shop girl	2	No occupation	2

DURATION OF THE DISEASE WHEN EXAMINED.

1 month or less	4 cases
1 to 3 months	0 "
4 to 6 months	0 "
7 months to a year	0 "
2 years	8 "
3 years	4 "
4 years	12 "
6 to 10 years	8 "
11 to 15 years	7 "
Over 15 years	7 "
Not stated	6 "

Prevalence of Sprue in Other Members of the Same Family. In 36 cases other members of the family were at the same time suffering from or had presumably had sprue. Sprue is undoubtedly a communicable disease, much as is tuberculosis, in this sense.

The Onset of Sprue. The investigation of these 68 cases has revealed what few if any works on sprue mention, namely, that the onset is often acute and can be dated from a severe "indigestion," "dyspepsia," or other acute and often violently inflammatory condition of some part of the upper intestinal tube. This is borne out by the following notes on the mode of onset in these cases:

As food poisoning	1 case
Acute, as gastro-enteritis	22 cases
Acute gastritis	1 case
Acute stomatitis	4 cases
Acute duodenitis	1 case
Total acute cases	29 cases
Cramps, nausea, bad taste in mouth	1 case
Lassitude, fever, sore throat	1 "
Anemia	1 "
Gradually, with gaseous indigestion	28 cases
No symptoms	1 case
Total beginning gradually	32 cases
Failed to remember how disease began	7 "

Type of the Disease. It is very evident that what we have been describing as "sprue" from the days of Hillary to date is really the terminal phase of sprue. In the *Am. Jour. Trop. Dis. and Preventive Med.*, July, 1915, vol. iii, No. 1, pp. 32-46, "Is Sprue a Moniliasis of the Digestive Tract?," the writer remarks, in connection with the prevalence of "chronic fermentative indigestion" in Porto Rico:

" . . . But many (cases) seem to me to be the début of that disease we call 'sprue,' and what I am rapidly coming to believe is merely the terminal phase of a condition commonly disappearing before reaching serious proportions, in this stage of début, as a rule easily controllable from a dietetic stand-point. . . . If we consider that a proportion of the many cases characterized by the 'chronic fermentative indigestion' described are really mild sprue, then we may believe that the disease is usually benign and tends to spontaneous cure."

That this is borne out by my experience here is beyond question.

Therefore, here we have again another point of resemblance to tuberculosis, a disease once only recognized in its ultimate stage, usually that of cachexia, all the preceding stages being covered by a series of glittering generalities, such as "chronic bronchitis," "broucheopneumonia," "grippe," etc., even to "malaria," diagnoses often prompted by whatever superficial condition the "clinical eye" might light on.

But in this series a strict accountability has been had in clinical appreciation: 50 of the 68 cases were complete sprue, incapable of being mistaken even by the dogmatic for any other disease; 18 were cases of incomplete sprue in which either the typical tongue, the typical stools, or the small liver were missing. That these were true sprue there is no reasonable doubt in my own mind, and I hope that there may be none in those who peruse these histories.

Of the 18 cases of incomplete sprue the tongue was always normal in 8; there was no history of diarrhea in 2; and in 12 the liver appeared normal. This organ was small in the other 56 cases. Cachexia was seen in 40 of the 68 cases; a decided sallow color in 10; in 18 no cachexia nor sallowness was observed.

Although the time is too short in the majority to record results of treatment, to date 24 have been apparently cured; 36 are improved, some notably and rapidly so; 6 are still unimproved; 1 was not treated; 1 has just begun treatment.

The type of the disease is expressed in these cases as follows:

Acute	3 cases
" moderate	1 case
" severe	2 cases
Subacute, mild	1 case
" moderate	1 "
" severe	2 cases
Chronic, mild	15 "
" moderate	12 "
" severe	19 "
" intense	8 "
Larval sprue	1 case
Carrier sprue	1 "
Convalescent from sprue	3 cases

CASES NOT SPRUE.

Cancer of the stomach	1 case
Chlorosis	2 cases
Chronic enterocolitis	3 "
Paralysis agitans	1 case
Rheumatic gout	1 "
Hypertrophy of the heart	1 "
Ulcer of leg	1 "
Tuberculosis of lungs	2 cases
Estivo-annual fever	2 "
Pellagra	4 "
Stomatitis, lipa	1 case
Syphilis	3 cases
" and alcoholism	1 case
Vitiligo	1 "
Neurasthenia	2 cases
Nervous dyspepsia	1 case
Gonorrhea	1 "

Of these cases, 8 stated that cases of sprue existed in their families, the rest denied the existence therein.

In 7 of the 32 the liver was distinctly small. In 13 only species of *Mouilia* other than *Mouilia psilosis* were isolated and yet the serological test with the antigens of *Mouilia psilosis* were absolutely negative, save in cases 25, 46, 56, and 59, two with + reactions and two with =.

As to pellagra and the deficiency theory there has been no confusion with that disease in this series, although the danger of such confusion is not to be overlooked when the skin lesions of pellagra are absent. Before the popular knowledge of the existence of pellagra in the United States, even among American physicians, Dr. W. W. King, Dr. Pedro Gutierrez and myself were conversant with its manifestations and reported, as the Porto Rico Anemia Commission, a case in our series for Picauiasis in 1901 (Anemia in Porto Rico, Government Printing Office, San Juan, P. R., December, 1901). Since that time we have had ample opportunity to observe that while present here it is by no means a common disease. Practically all of the people of Porto Rico eat beans in plenty, no matter how poor or how rich, and this is one of the first lessons the tourist learns, a fact to which our attention was especially directed by Dr. Michel, who has worked intensely on pellagra in the South of the United States and who is as decided as we are that pellagra is not a common disease in Porto Rico. Meat was a common article of diet among the cases which form the basis of this paper, and I have purposely assured myself that the full 95 per cent. could not be taxed with the charge that vitamins were lacking in their diet. It would have to be some mysterious sort of vitamin if such lack existed. Of course, the writer has not lost sight of the justifiable suspicion in connection with food imbalance in that lack of unidentified vitamins or excess of certain classes of foods may tremendously affect the manifestations of chronic infectious processes initiated and sustained by organisms of comparatively little potency. The epochal work on vitamin deficiency seems to be as yet in its infancy.

The skin manifestations of pellagra were missing and the mental symptoms were not comparable to those of pellagra, save in one case. It is not therefore to be ignored that we of this institute who live our medical life here quite as intensely as our confrères in the North, who are unconversant with our local problems, are willing to be deceived by so gross an error in observation. Quite on the contrary the cases of pellagra are clearly diagnosed in this series, and they are all negative for *Mouilia psilosis*, and all but one (a faint positive) are negative also when submitted to the Wassermann test for sprue. That cases of "pellagra sine pellagra" exist—cases by the way which are violently contested by authorities on pellagra—can only be resolved, I believe, by accepting the etiology of sprue as herein recorded and thus clearing up a question until now unanswered.